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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ADVISORY ACTION

1. Claims 21, 28, 40, 43, 99-104, 107-113, 120-135, 137-143 are pending.

2. The request for entering amendments to claim 28, 40 and arguments filed on 12/11/2008 under 37 CFR 1.116 in reply to the Final Action mailed on 11/14/2008 are acknowledged. The proposed amendments to the claims will be entered. The amendments to these claims obviate the previous 35 USC 112, first paragraph rejection made on claims 28, 40, 103, 107-108 as these claims are now limited to isolated mammalian cells. As such, this rejection is hereby withdrawn. However, the amendments and arguments are not deemed sufficient to overcome the art rejection of claims 21, 28, 40, 99-104, 107-108 under 35 USC 103(a) previously introduced.

3. Applicant argues that the standard for determining obviousness is not whether the references explicitly teach away from the claimed invention but rather whether the cited references established that the claimed invention is a predictable use of known prior art elements. According to Applicant not all elements of the claims are set forth in the references and there is no evidence that one of skill in the art would have been motivated to select a zinc finger nuclease and the donor polynucleotide for placement on the same vector. It is Applicant's contention that the explanation given by the Examiner is unsupported by any evidence except for Applicant's own specification. Applicant argues that none of the cited references teach or suggest using a single vector and that without the teachings of the specification, one of skill in the art would have absolutely no expectation that a single vector would be advantageous.

4. Applicant's arguments have been fully considered but are not deemed persuasive. The Examiner acknowledges applicant's statement in the specification regarding the advantages of using a single delivery vector as well as the fact that the references cited do not teach the use of a single vector to deliver both the nucleic acid encoding the nuclease and the repair substrate. However the Examiner strongly disagrees with applicant's contention that one of skill in the art would have not recognized the advantages of delivering a single vector instead of two without reading applicant's specification because,

as extensively discussed in the previous Office actions, it is essentially simpler to deliver one vector instead of two to a cell. Thus, contrary to Applicant's assertions, one of skill in the art without any prior knowledge of Applicant's specification would have reached the conclusion that using a single vector instead of two vectors is desirable and, at a minimum, would have been motivated to try to use a single vector to deliver both nucleic acids.

5. Applicant further argues that there is no one shred of evidence presented by the Examiner that the inserted chromosomal targets are not different from endogenous chromosomal targets. According to Applicant, the evidence of record establishes that cleavage of non-endogenous chromosomal targets is not at all predictive of cleavage of endogenous chromosomal targets as claimed, citing paragraph [0160] of the specification. Applicant submits that the target used by Choulika et al. was not endogenous to a mammalian genome and that the reference by Porteus et al. (Nature Biotechnology 23:967-973, 2005; Exhibit A) discloses that the major limitation in using homing endonucleases in gene targeting is the lack of recognition sites for them in mammalian genes. Furthermore, applicant argues that Choulika et al. is not an enabling reference with regard to engineered zinc finger proteins and/or modified homing nucleases and that there is no disclosure by Choulika et al. as to how to engineer a ZFP to bind a selected endogenous target site. Applicant further cites Bibikova et al. and points out that Bibikova et al. were not sure if zinc finger nucleases would result in targeting of endogenous chromosomal DNA by a repair substrate.

6. Applicant's arguments have been fully considered but are not deemed persuasive. As previously indicated, the examiner acknowledges that Choulika et al. and Bibikova et al. teach the insertion of a SceI target site in the chromosome. The Examiner also acknowledges the teachings of the Porteus et al. reference. However, while neither Choulika et al. nor Bibikova et al. explicitly teach engineering zinc finger proteins to recognize endogenous chromosomal sequences, the teachings of art prior to the filing date of the instant application provide a great deal of information as to how to engineer zinc finger DNA

binding domains to bind to <u>any</u> selected target site, as extensively discussed by Applicant in the remarks section of the response filed on 8/6/2008. See, specifically, pages 11-13 of the response reproduced below.

Moreover, the specification and state of the art clearly teach that these structurally-related zinc finger DNA-binding domains can be modified in their recognition helices so as to recognize any selected target site (see, e.g., paragraphs [0100] and [0165] of the as-filed specification):

> Various methods for designing chimeric nucleases with varied DNA recognition sequences are known in the art. In certain embodiments, the DNA binding domain comprises one or more zinc finger domains (or referred to as zinc fingers). The zinc fingers can be engineered to recognize a selected target site in the target sequence. As described above, Cys_2His_2 proteins may be engineered to recognize a wide variety of sites. As another example, zinc fingers can be selected by using polypeptide display libraries. The target site is used with the polypeptide display library in an affinity selection step to select variant fingers that bind to the target site. Typically, constant zinc fingers and fingers to be randomized are made from any suitable C_2H_2 zinc finger protein, such as SP-1, SP-1C, TFIIIA, GLI, Tramtrack, YY1, or
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> ZIF268 (see, e.g., Jacobs, EMBO J. 11:4507 (1992); Desjarlais & Berg, Proc. Natl. Acad. Sci. U.S.A. 90:2256-2260 (1993)). The polypeptide display library encoding variants of a zinc finger protein comprising the randomized finger, one or more variants of which will be selected, and, depending on the selection step, one or two constant fingers, is constructed according to the methods known to those in the art. Optionally, the library contains restriction sites designed for ease of removing constant fingers, and for adding in randomized fingers. Fingers are randomized, e.g., by using degenerate oligonucleotides, mutagenic cassettes, or error prone PCR. See, for example, U.S. Pat. Nos. 6,326,166, 6,410,248, and 6,479,626.
>
> Chimeric nucleases are modular in nature with the DNA binding specificity residing in the zinc finger domain. By modifying the DNA binding specificity of the zinc finger domain, they can be engineered and optimized to bind specifically to a wide variety of nine bp sequences (Rebar et al., 1994, Science, 263:671-3; Wolfe et al., 2001, Structure (Camb), 9:717-23; Sera and Uranga, 2002, Biochemistry, 41:7074-81). Thus, one should be able to engineer chimeric nucleases to stimulate gene targeting at any locus.

The state of the art also evidences that, at the time of filing, the skilled artisan knew how to alter the structure of any zinc finger DNA-binding domain so as to bind to any pre-selected target site (See, U.S. Patent No. 6,534,261 (Issued March 18, 2003; Reference AQ of IDS mailed on February 13, 2004) at column 15, lines 7-17):

> The ZFPs of the invention are engineered to recognize a selected target site in the endogenous gene of choice. Typically, a backbone from any suitable C2H2 ZFP, such as SP-1, SP-1C, or ZIF268, is used as the scaffold for the engineered ZFP (see, e.g., Jacobs, EMBO J. 11:4507 (1992); Desjarlais & Berg, PNAS 90:2256-2260 (1993)). A number of methods can then be used to design and select a ZFP with high affinity for its target (e.g., preferably with a Kd of less than about 25 nM). As described above, a ZFP can be designed or selected to bind to any suitable target site in the target endogenous gene, with high affinity.

See, also, U.S. Patent No. 6,013,453 (Issued January 11, 2000; Reference AK of IDS mailed on February 13, 2004) at column 2, lines 48-54:

> Protein engineering experiments have shown that it is possible to alter rationally the DNA-binding characteristics of individual zinc fingers when one or more of the α-helical positions is varied in a number of proteins [references omitted].

Methods of engineering zinc finger DNA-binding domains to bind to any selected target site are also described, in detail, in WO 01/66717 (reference BP of IDS filed February 10, 2006); WO 01/40798 (reference BQ of IDS filed February 10, 2006); and WO 02/04488 (reference BR of IDS filed February 10, 2006).

Thus, the specification and references of record clearly establish that the common structural features to be modified in a zinc finger DNA-binding domain such that it can recognize any selected DNA target were well known at the time of filing. Specifically, the structure of zinc finger proteins, as well as how to alter this structure (amino acid sequence of the recognition helices) to obtain zinc finger proteins that bind to a selected target site are amply described in the specification and art.

7. Thus, while the prior art does not specifically provide examples of engineered zinc finger proteins that bind to endogenous chromosomal sequences, the prior art as indicated above, clearly teaches how to engineer zinc finger proteins that bind to any desired target, including endogenous chromosomal targets. As previously discussed, it is clear from the teachings of Choulika et al. and Bibikova et al. that the purpose of introducing the SceI target site in the chromosome was to demonstrate the principle of targeting the chromosome of a host cell for repair. Therefore, the "endogenous" limitation is at a

minimum suggested by the cited references and the teachings of the prior art as cited by Applicant would have provided one of skill in the art with the knowledge required to engineer the zinc finger DNA binding domain to recognize an endogenous chromosomal target. Thus, for the reasons of record and those set forth above, the claimed invention is deemed obvious over the teachings of the prior art.

8. For purposes of Appeal, the status of the claims is as follows:

Claim(s) rejected: 21, 28, 40, 99-104, 107-108

Claim(s) withdrawn from consideration: 43, 109-113, 120-135, 137-143

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez
Primary Patent Examiner
Art Unit 1652

DR
January 10, 2009